



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

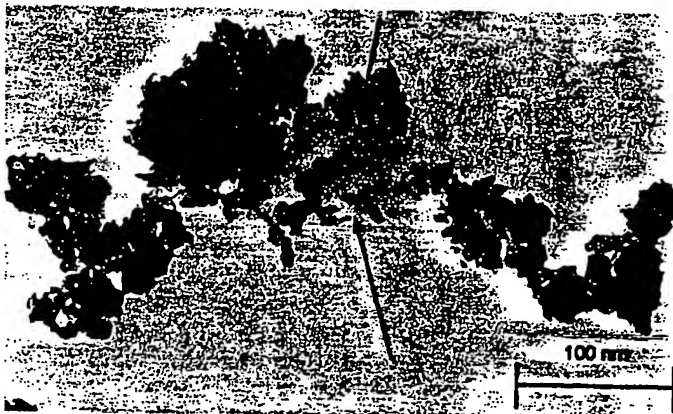
(51) International Patent Classification ⁶ : A61L 27/00		(11) International Publication Number: WO 98/16268
A3		(43) International Publication Date: 23 April 1998 (23.04.98)
(21) International Application Number: PCT/US97/18631 (22) International Filing Date: 16 October 1997 (16.10.97) (30) Priority Data: 08/732,016 16 October 1996 (16.10.96) US 08/729,344 16 October 1996 (16.10.96) US 08/729,343 16 October 1996 (16.10.96) US (71) Applicant (for all designated States except US): ETEX CORPORATION [US/US]; 38 Sidney Street, Cambridge, MA 02138 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LEE, Dosuk, D. [US/US]; Apartment 518, 50 Longwood Avenue, Brookline, MA 02146 (US). REY, Christian [FR/FR]; Lieu-dit "Les Dames", Aureville, F-31320 Castanet (FR). AIOLOVA, Maria [BG/US]; 123 Seawall Avenue, Brookline, MA 02146 (US). (74) Agent: SCOZZAFAVA, Mary, Rose; Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA 02109 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 July 1998 (30.07.98)

(54) Title: METHOD OF PREPARING A POORLY CRYSTALLINE CALCIUM PHOSPHATE AND METHODS OF ITS USE

(57) Abstract

The present invention provides a novel process for producing a calcium phosphate cement or filler which hardens in a temperature dependent fashion in association with an endothermic reaction. In the reaction a limited amount of water is mixed with dry calcium phosphate precursors to produce a hydrated precursor paste. Hardening of the paste occurs rapidly at body temperature and is accompanied by the conversion of one or more of the reactants to poorly crystalline apatitic calcium phosphate. The hardened cements, fillers, growth matrices, orthopedic and delivery devices of the invention are rapidly resorbable and stimulate hard tissue growth and healing. A composite material is provided including a strongly bioresorbable, poorly crystalline apatitic calcium phosphate composite and a supplementary material.

The supplementary material is in intimate contact with the hydroxyapatite material in an amount effective to impart a selected characteristic to the composite. The supplemental material may be biocompatible, bioresorbable or non-resorbable. A method for treating a bone defect also is provided by identifying a bone site suitable for receiving an implant, and introducing a strongly resorbable, poorly crystalline apatitic calcium phosphate at the implant site, whereby bone is formed at the implant site. The implant site may be a variety of sites, such as a tooth socket, non-union bone, bone prosthesis, an osteoporotic bone, an intervertebral space, an alveolar ridge or a bone fracture.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/18631

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 037 639 A (TUNG MING S) 6 August 1991 cited in the application see claims; examples 1-5 ---	1-5
P,X	WO 96 36562 A (ETEX CORP) 21 November 1996 cited in the application see claims; examples ---	1-5
P,X	WO 97 17285 A (ETEX CORP) 15 May 1997 cited in the application see claims ---	1-5
Y	WO 92 02453 A (NORIAN CORP) 20 February 1992 see claims ---	1-89

	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

29 May 1998

Date of mailing of the international search report

19. 06. 1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

ESPINOSA, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/18631

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 02412 A (UNIV READING ;SIMKISS KENNETH (GB); TAYLOR MARINA GLORIA (GB)) 3 February 1994 see claims ---	1-89
Y	WO 94 04657 A (UNIV PENNSYLVANIA) 3 March 1994 see claims ---	1-89
A	YASUE T ET AL: "EFFECT OF ADSORPTION OF SUCCINIC ACID ON THE FORMATION OF AMORPHOUS CALCIUM PHOSPHATE" JOURNAL OF THE CERAMIC SOCIETY OF JAPAN, INTERNATIONAL EDITION, vol. 102, no. 12, 1 December 1994, pages 1125-1130, XP000505560. ---	1
A	WO 95 08319 A (AMERICAN DENTAL ASS) 30 March 1995 see claims & US 5 525 148 A cited in the application ---	1
A	EP 0 347 028 A (NORIAN CORP) 20 December 1989 see claims; examples & US 4 880 610 A cited in the application ---	1
A	EP 0 520 690 A (NITTA GELATIN KK) 30 December 1992 see claims; examples -----	1

INTERNATIONAL SEARCH REPORT

I. national application No.
PCT/US 97/18631

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 67-83, 88-89 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/18631

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5037639 A	06-08-1991	US 5437857 A	01-08-1995
		US 5534244 A	09-07-1996
		US 5268167 A	07-12-1993
		US 5460803 A	24-10-1995
WO 9636562 A	21-11-1996	US 5676976 A	14-10-1997
		AU 5865996 A	29-11-1996
		EP 0825963 A	04-03-1998
		FI 974210 A	09-01-1998
		NO 975247 A	09-01-1998
		US 5650176 A	22-07-1997
		US 5683461 A	04-11-1997
WO 9717285 A	15-05-1997	AU 7723596 A	29-05-1997
WO 9202453 A	20-02-1992	AT 157329 T	15-09-1997
		CA 2088169 A	28-01-1992
		DE 69127447 D	02-10-1997
		DE 69127447 T	29-01-1998
		EP 0541687 A	19-05-1993
		JP 5509284 T	22-12-1993
		US 5178845 A	12-01-1993
WO 9402412 A	03-02-1994	AU 4579893 A	14-02-1994
		ZA 9305231 A	22-12-1993
WO 9404657 A	03-03-1994	CA 2142282 A	03-03-1994
		EP 0672117 A	20-09-1995
		JP 8500248 T	16-01-1996
		US 5643789 A	01-07-1997
		US 5648301 A	15-07-1997
		US 5676720 A	14-10-1997
WO 9508319 A	30-03-1995	US 5525148 A	11-06-1996
		DE 721320 T	10-04-1997
		EP 0721320 A	17-07-1996
		ES 2099687 T	01-06-1997
		JP 10504467 T	06-05-1998
EP 0347028 A	20-12-1989	US 4880610 A	14-11-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/18631

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0347028 A		CA 1332495 A	18-10-1994
		JP 2022113 A	25-01-1990
		US 5047031 A	10-09-1991
		US 5129905 A	14-07-1992
		US 5053212 A	01-10-1991
		US 5178845 A	12-01-1993
		US 5336264 A	09-08-1994
EP 0520690 A	30-12-1992	DE 69205736 D	07-12-1995
		DE 69205736 T	13-06-1996
		JP 5168692 A	02-07-1993
		JP 7034816 B	19-04-1995
		US 5342441 A	30-08-1994